REMARKS

Claims 7 and 12-17 are pending and stand ready for further actions on the merits. Support for new claim 12 can be found on page 8, lines 6-8. Support for new claim 13 can be found in claim 4. Support for new claim 14 can be found on page 9, line 3. Support for new claim 15 can be found on page 9, line 4. Support for new claims 16 and 17 can be found in claims 3 and 5 and on page 29, line 11. No new matter has been added by way of the above-amendment.

Issues under 35 U.S.C. 102

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Kaspersen et al. (Journal of Label. Comp. and Radiopharm., 27, No. 9, 1055 (1989)). Applicants respectfully traverse the rejection.

Mirtazapine has been sold as a pharmaceutical useful as an antidepressant in many countries including the United States. It is apparent from the whole disclosure of the instant specification that the object of the present invention is to provide pharmaceuticals useful as antidepressant for therapeutic application (see, *inter alia*, page 1, lines 11-15 of the instant specification). In other words, the ultimate object of the present invention is to provide low hygroscopic crystals of mirtazapine

useful as therapeutic agents, which are prepared by drying the crystals of a mirtazapine hydrate of inventive formula (I).

Accordingly, the crystals of a mirtazapine hydrate of inventive formula (I) are well suited as an intermediate for the antidepressant therapeutic agent which are low hygroscopic crystals of mirtazapine.

Kaspersen et al. disclose the preparation of labeled compounds. Kaspersen et al. also disclose that:

> "[f]or metabolic studies in animal and man and for the determination of the bioavailability, the compound labeled with ^{3}H, ^{14}C, and ^{13}C was needed."

Thus, it was an object for preparing the labeled compounds (see page 1055, item "INTRODUCTION"). In other words, it is thought that the labeled compounds prepared by Kaspersen et al. are to be administered a single time for studies. There is no teaching or suggestion that the labeled compounds are continuously administrated to a patient as a therapeutic substance.

Also, there is clearly no need to use the labeled compounds as pharmaceuticals for humans, and there is no particular advantage in using the labeled compounds as a therapeutic substance. Moreover, if the labeled compounds are administered to humans, it is possible that the continuous administration of labeled compounds could bring unwanted side effects. For instance, it is evident that the

"compound 1d" pointed out by the Examiner is not suitable for the therapeutic agent since the "compound 1d" has a radioactive isotope of ^{14}C.

Indeed, Kaspersen et al. disclose:

> "Org 3770(1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine; (Figure 1) is a potential antidepressant drug under clinical development..."

in the "INTRODUCTION" section of pages 1055-6. This compound of Figure 1 is the only compound identified by Kaspersen et al. as having a therapeutic effect. On the contrary, the Examiner relies on the disclosure of Kaspersen et al. relating to the process for preparing the labeled compounds in finding that the mirtazapine hydrate of inventive formula (I) anticipated. For example, the compound at page 1058, Fig. 4, which is pointed by the Examiner, is abbreviated as "[$^{13}C_6$]-Org 3770" and denoted as the number of the compound "1c". Also, the compound at page 1067 is abbreviated as "[10-^{14}C]-Org 3770" and denoted as the number of the compound "1d". Kaspersen et al. do not fairly suggest using these labeled compounds in treatment.

The crystals of a mirtazapine hydrate of the present invention should be suited for the intermediate of the therapeutic agent as mentioned above. Therefore, the present invention is not intended to provide a labeled compound, and the crystals of the mirtazapine

hydrate of the present invention merely contain the isotope in a naturally occurring content. This is evident from the characteristics of pharmaceuticals for therapeutic application and the whole disclosure of the instant specification.

As explained above, the mirtazapine hydrate is quite different from the labeled compounds disclosed by Kaspersen et al.

According to the present invention, anhydrous mirtazapine having a high purity can be prepared by drying the crystals of the mirtazapine hydrate (see page 8, lines 12-14 of the instant invention). When drying the crystals of the mirtazapine hydrate, the drying can be efficiently carried out by previously pulverizing the crystals of the mirtazapine hydrate before drying (see page 8, lines 18-20 of the instant invention).

Although Kaspersen et al. disclose hydrous compounds, they do not disclose or suggest that anhydrous mirtazapine is prepared by pulverizing the mirtazapine hydrate and thereafter drying the pulverized mirtazapine hydrate. Therefore, there is no motivation in Kaspersen et al. to arrive at the present invention.

Since Kaspersen et al. have intended to provide labeled compounds for metabolic studies, there is no teaching or suggestion to use the compounds in the preparation of the therapeutic anhydrous mirtazapine.

As explained above, since Kaspersen et al. do not disclose or suggest that the crystals of the mirtazapine hydrate are

pulverized, the present invention according to claim 13 was not in the possession of Kaspersen et al.

Regarding the inventions of claims 14 and 15, drying of the crystals of the mirtazapine hydrate is efficiently carried out because the crystals are previously pulverized to an average particle diameter of 10 to 70 μm, preferably 20 to 60 μm (see page 9, lines 1-4 of the instant specification). However, Kaspersen et al. fail to teach or suggest this drying step. Therefore, the claimed invention according to claims 14 and 15 was not in the possession of Kaspersen et al.

In view of foregoing, Applicants respectfully submit that Kaspersen et al. fail to anticipate the presently claimed invention and withdrawal of the rejection is respectfully requested.

Drawings

Applicants note that ten (10) sheets of drawings have been with this application. However, the Examiner has not indicated that the drawings are acceptable. Applicants respectfully request that the Examiner indicates in the next communication whether the drawings are acceptable.

Conclusion

In view of the above amendments and comments, Applicants respectfully submit that the claims are in condition for allowance. A notice to such effect is earnestly solicited.

Applicant respectfully petitions under the provisions of 37 CFR 1.136(a) and 1.17 for a three-month extension of time in which to respond to the Examiner's Office Action. The Extension of Time Fee in the amount of $930.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Garth M. Dahlen, Ph.D. (Reg. No. 43,575) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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